REMARKS

Claims 82-150 are currently pending in the application. Only claims 82, 115, 146, and 149 are in independent form.

The Office Action states that the drawings are objected to for the reasons set forth in attached PTO 948 Form. The appropriate corrections will be made upon allowance of the present application.

The Office Action states that the application does not contain an abstract of the disclosure as is required. An abstract, on a separate sheet of paper, is attached hereto.

The Office Action states that titles for the various part of the application are required. The appropriate correction has been made herewith, such that all of the appropriate section headings have been listed.

Claims 82-150 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that the term "relative" in claims 82 and 94 is a relative term which renders the claims indefinite. Accordingly, in order for further prosecution, claims 82 and 94 have been amended to more specifically recite this relationship. Reconsideration of the rejection is respectfully requested.

The Office Action states that in claim 105 the recitation of "first and second antibodies" lacks antecedent basis. In order for further prosecution, the claim

has been amended to recite proper antecedent basis. Reconsideration of the rejection is respectfully requested.

The Office Action states that some of the claims utilize the phrase "substantially" and this phrase renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. In order for further prosecution, the phrase "substantially" has been removed from all of the claims, thus rendering the claims definite. Reconsideration of the rejection is respectfully requested.

Claims 82, 146, and 149 stand rejected under U.S.C. 35 § 103(a) as being unpatentable over the Bergman patent in view of the May et al patent. Reconsideration of the rejection is respectfully requested.

The Office Action states that the Bergman patent teaches a method for detecting the presence of autoantibodies in biological fluids, such as serum (column 3, line 67). Also, according to the Office Action, the Bergman patent teaches providing an antigen specific for autoantibodies such as thyroid peroxidase, providing a substrate having an immobilized antibody to antigen, contacting antigens with body fluid samples to allow binding of the complex, the mixture is allowed to flow into test tubes to contact with the immobilized monoclonal antibody, providing a labeling means such as labeled non-immobilized mobile monoclonal antibody to allow binding of the complex, and an indication of the presence of autoantibodies and a sample of body fluid (Figure 1, column 3 and 4). The Office Action states that the Bergman patent teaches various methods of detection of autoantibodies including three different

competitive situations involving analyte antibody analysis. The Bergman patent, according to the Office Action does not teach the use of the method of the invention on a test strip substrate. However, the Office Action states that the May et al patent teaches a test strip format in which assays involving specific binding of amino acids may be formatted in a test strip to provide convenience for home or clinical use. The Office Action concludes that it would be obvious to one with ordinary skill in the art to modify the method of the Bergman patent by incorporating the method to a test strip device as taught of the May et al patent because test strip devices are intended to be used for rapid analytical results with the least degree of skill and involvement from the user.

The Bergman patent describes an immunological assay method for screening for autoantibodies in a biological fluid, in particular it describes a method for screening autoantibodies to thyroid peroxidase TPO. These assays are of the competitive type wherein antibodies to TPO compete with the binding of the antibody TPO with one a labeled non-immobilized antibody and/or to an immobilized antibody. More specifically, at lines 42-52 in column 6, the Bergman patent specifies that the solid substrate and conditions employed in the immunological reaction do not "differ fundamentally from other conventional immunological assay methods." Furthermore, the examples of the Bergman patent clearly describe the incubation of the above described reagents and it is evident that the use of the subject immunological assay techniques as employed therein used known methods.

With regard to the May et al patent, it describes that a capillary immunoassay test device. This general test device includes a hollow casing

containing a dried porous carrier. A liquid test sample can be applied to a bibulous sample receiving member and permeate therefrom to the porous carrier, the carrier including a first zone containing a labeled binding reagent which is fully mobile within the porous carrier when moistened, and a second zone, spaced away from the first zone, containing an unlabeled specific binding reagent for analyte. The unlabeled reagent is permanently immobilized on the carrier material and therefore is mobile when moistened. In other words, the zones of the carrier material are arranged such that the liquid sample applied to the porous carrier can permeate via the first zone to the second zone. The reagents and analytes for use in a test device such as this can be employed in either sandwich or competition type reactions. The May et al patent further teaches that both the above referred to binding reagents can be antibodies to analytes such as hCG and LH. For example, in the case of the analyte being the pregnancy hormone hCG, the mobile binging reagent can be highly specific anti-hCG antibody and the immobilized binding reagent can be a further specific anti-hCG antibody, where the anti-hCG antibodies have specificities for different hCG epitopes.

Whilst the Examiner's comments in the Office Action that May et al patent teaches 'the use of test strip devices are intended for rapid analytical results with the least degree of skill and involvement from the user' are accepted, this in no way provides a basis for combining the teachings of the Bergman and May et al patents as is suggested by the Examiner.

To the contrary, at the priority date of the present invention, nowhere in the prior art was there any teaching whatsoever as to the provision of assay methods and diagnostic kits for simple and rapid monitoring of autoantibodies. This

is the nub of the present invention: namely the unsolved need that was faced by the inventors at the priority date of the present invention was the provision of assay methods and diagnostic kits for simple and rapid monitoring of autoantibodies and this has now been achieved by methods and kits as defined in the claims currently pending in this application. Nowhere in the prior art was there any hint or suggestion of such rapid monitoring of autoantibodies or that such rapid monitoring of autoantibodies might be possible.

The present invention also provides, for the first time, assay methods and diagnostic kits for the monitoring of autoantibodies that can be carried out near the point of patient care by personnel who do not have experience in laboratory procedures. Assay methods and diagnostic kits of this type for monitoring of autoantibodies as achieved by the present invention were in no way contemplated, or least of all suggested, by the prior art. To the contrary, prior art assay methods for monitoring autoantibodies, such as for example described in Bergman, were carried out remote from the point of patient care in specially equipped laboratories, could only be carried out by experienced personnel and took several hours to complete.

The simple and rapid monitoring of autoantibodies as is now achieved by the present invention in turn allows the simple and rapid diagnosis of autoimmune disease. In particular, the present invention provides assay methods and kits that can provide rapid, simple and accurate monitoring of autoantibodies that can in turn provide rapid, simple and accurate diagnosis of the following autoimmune diseases in a way that could not have been achieved by the prior art - autoimmune thyroid

disease (for example, hypothyroidism, or hyperthyroidism), type I diabetes, celiac disease, myasthenia gravis, systemic lupus erythematosus and the like. It is of course extremely beneficial to be able to rapidly monitor autoantibodies as is achieved by the present invention so as to be able to diagnose such diseases as above.

The advantages associated with the present invention as set forth in the presently pending independent claims provide a solution to a long term problem pertaining to the ability to obtain rapid detection of autoantibodies. The advantages of the present invention are indicative of non-obviousness. These advantages taken together with the specific differences between the claims as pending and the prior art as set forth below demonstrate that the invention as set forth in the presently pending independent claims are patentable over the prior art.

The inventiveness of assay methods and diagnostic kits as defined in the claims currently pending in this application can be further seen if the following recognised criteria for evaluating obviousness are applied to the cited prior art and the claims currently pending in this application:

- The scope and content of the prior art should be determined;
- The differences between the prior art and the claims currently pending in this application should be ascertained;
- The level of skill in the art should be resolved, so as to obtain a realistic picture of how a skilled addressee faced with the prior art would have proceeded at the priority date of the present invention.

With specific regard to differences between the cited prior art and the present invention, the Bergman patent as disclosed above relates to the use of conventional test tube immunological reaction conditions for screening for autoantibodies to TPO which require incubation involving the reagents employed

therein. There is no disclosure in the Bergman et al patent for the assay techniques to be modified to enable rapid and simple detection of autoantibodies. In particular, there is no suggestion that a mixture of an antigen and the sample of body fluid could be allowed to flow along a substrate, so as to be able to interact with an antibody immobilized to the substrate as is required by the presently pending independent claims. In actuality, it would be contrary to the teaching provided by the Bergman patent to do so.

With regard to the May et al patent, it relates to a capillary immunoassay test device. There is no disclosure in the May et al patent for providing an antigen source which, together with the sample of body fluid, could flow along a substrate so as to be able to interact with an antibody immobilized substrate, providing labeling means that would monitor binding of autoantibodies and the antigen, monitoring the binding so as to provide an indication of the level of autoantibodies in the sample of body fluid as is set forth in the presently pending independent claims. More specifically, the May et al patent instead describes the use of antibodies as specific binding reagents for an analyte which is quite different from that disclosed in the presently pending independent claims in which the purpose is to actually screen for antibodies.

In order to arrive at the presently pending independent claims, a person of skill in the art would need to take the following steps; first, one would have to take the Bergman patent and decide to modify the incubation immobilization techniques specifically taught therein. However, there is no suggestion for one of skill in the art that the assay techniques described in the Bergman patent could be modified to

not united

enable a rapid and simple detection of autoantibodies. There is nothing disclosed in the Bergman patent which would have lead one of skill in the art to provide a mixture of an antigen and a sample of body fluid that could be allowed to flow along a substrate so as to be able to enact with an antibody immobilized to the substrate as is required by the presently pending independent claims. Then despite the teaching to the contrary in the Bergman patent one of skill in the art would have to decide to modify the incubation and binding conditions of the Bergman patent to be more along the lines of a capillary immunoassay test device. There is no suggestion in the Bergman patent nor the May et al patent for such a modification or that such a modification is even desirable, nor is it taught how such modifications might be achieved. Additionally, the process of moving from a standard test tube incubation to a capillary immunoassay test device for screening for autoantibodies is not straight forward and would require numerous modifications.

Finally, even had one of skill in the art decided to modify the teaching of the Bergman patent toward a capillary immunoassay test device, the individual would not have been aided by utilizing the May et al patent. This is because the test device taught the May et al patent specifically employes antibodies as a specific binding reagent and would therefore require considerable further input to develop the methods of the presently pending independent claims. There is no teaching nor suggestion in either the Bergman patent or the May et al patent either above or in combination for the methods of the presently pending independent claims. Additionally even if one were to combine the May et al patent and the Bergman patent one would not obtain the methods of the presently pending independent claims. Accordingly, the claims are

patentable over the Bergman patent and the May et al patent and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: September 13, 2001

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on September 13, 2001.

Marie M. DeWitt

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 1, after the Title, please insert the following headings:

-- **BACKGROUND OF THE INVENTION**

1. Field of the Invention --

The present invention is concerned with assays for screening a sample of body fluid for autoantibodies to various antigens. In particular, the present invention is concerned with screening a sample of body fluid for autoantibodies associated with autoimmune thyroid disease.

Page 1, line 8, please insert the following heading:

-- **2. Description of Related Art** --

Autoimmune diseases are characterized by the presence of...

Page 5, line 7, please insert the following heading:

-- **SUMMARY OF THE INVENTION** --

According to the present invention, ...

Page 25, line 29, please insert the following heading:

-- **BRIEF DESCRIPTION OF THE DRAWINGS** --

The present invention will now be illustrated with ....

Page 27, line 20, please insert the following heading:

-- **DETAILED DESCRIPTION OF THE INVENTION** --

Referring firstly to Figure 1a and 1b, there is shown a ...

IN THE CLAIMS:

82. A method of screening a sample of body fluid for at least one autoantibody to at least one antigen, which method comprises:

(a) providing a source of said at least one antigen to said autoantibody;

(b) providing a substrate having immobilized thereto at least one antibody to said antigen of step (a);

(c) contacting said antigen source of step (a) with said sample of body fluid, so as to obtain a mixture wherein said antigen is allowed to [substantially] bind with said autoantibody, when the latter is present in said sample;

(d) allowing said mixture obtained in step (c) to flow [relative] along [to] said substrate of step (b) [so as to allow said mixture to contact] and to interact with said antibody immobilized to said substrate;

(e) providing labeling means so as to permit monitoring of binding of said autoantibody and said antigen present in said mixture obtained in step (c); and

(f) monitoring said binding so as to provide an indication of the presence of said autoantibody in said sample of body fluid.

87. A method according to claim 82, which comprises contacting in step (c) said antigen source and said sample of body fluid with at least one [substantially] non-immobilized antibody to said antigen.

88. A method according to claim 87, wherein said non-immobilized antibody is provided in [substantially] purified form.

94. A method according to claim 93, wherein at least said sample of body fluid is contacted with an application zone of said substrate, which application zone is provided upstream of said immobilized antibody on said substrate [relative to said immobilized antibody,] and wherein said mixture is allowed to flow from said application zone along said substrate so as to interact with said immobilized antibody.

96. A method according to claim 94, wherein said application zone further includes at least one [substantially] non-immobilized antibody to said antigen, and said mixture in step (c) is obtained by contacting said sample of body fluid and said antigen with said non-immobilized antibody present in said application zone.

97. A method according to claim 94, wherein said antigen source of step (a) and said sample of body fluid are contacted [substantially] remote from said substrate so as to provide said mixture of step (c), and said mixture is subsequently contacted with said application zone.

98. A method according to claim 97, wherein [at least one reagent selected from] said antigen source of step (a), said sample of body fluid and at least one [substantially] non-immobilized antibody to said antigen, [is] are contacted [substantially] remote from said substrate so as to provide said mixture of step (c), and said mixture is subsequently contacted with said application zone.

100. A method according to claim 82, wherein said immobilized antibody is in [substantially] purified form.

104. A method according to claim 103, wherein said antigen includes a binding site to which either said autoantibody or said immobilized antibody can bind, whereby in step (d) binding of said immobilized antibody to said binding site is [substantially] precluded where said autoantibody has [substantially] bound to said

binding site in step (c).

105. A method according to claim 82, which comprises screening said sample of body fluid for at least a first and a second autoantibod[ies]y to said antigen, wherein at least first and second antibodies to said antigen are immobilized on said substrate in step (b).

106. A method according to claim 105, wherein said antigen includes:

a first binding site to which either said first autoantibody or said first immobilized antibody can bind, whereby in step (d) binding of said first immobilized antibody to said first binding site is [substantially] precluded where said first autoantibody has [substantially] bound to said first binding site in step (c); and

a second binding site to which either said second autoantibody or said second immobilized antibody can bind, whereby in step (d) binding of said second immobilized antibody to said second binding site is [substantially] precluded where said second autoantibody has [substantially] bound to said second binding site in step (c);

wherein said first and second binding sites are [substantially] distinct sites on said antigen.

109. A method according to claim 87, wherein said non-immobilized antibody is provided with said labeling means, which non-immobilized antibody is capable of binding to a site on said antigen [substantially] distinct from a binding site for either (i) said autoantibody or autoantibodies being screened or (ii) said immobilized antibody, whereby in step (d), antigen is allowed to be [substantially] bound both to said immobilized antibody and to said non-immobilized antibody.

110. A method according to claim 87, which comprises screening said sample of body fluid for at least first and second autoantibodies to said antigen, wherein said non-immobilized antibody is capable of binding to a site on said antigen to which either said first or second autoantibody can bind and which is [substantially] distinct to a binding site on said antigen for said immobilized antibody, whereby in step (d) antigen is allowed to be [substantially] bound both to said immobilized

antibody and to said non-immobilized antibody.

111. A method according to claim 110, wherein said antigen includes:

a first binding site to which either said first autoantibody or said immobilized antibody can bind, whereby in step (d) binding of immobilized antibody to said first binding site is [substantially] precluded where said first autoantibody has [substantially] bound to said first binding site in step (c); and

a second binding site to which either said second autoantibody or said non-immobilized antibody can bind;

wherein said first and second binding sites are [substantially] distinct sites on said antigen.

114. A method according to claim 87 which further comprises a positive control that is present in the presence or absence of the autoantibody or autoantibodies being screened, wherein the positive control comprises attaching to the substrate at least one control agent that can bind to the at least one [substantially] non-immobilized antibody.

115. A kit for use in screening a sample of body fluid for at least one autoantibody to at least one antigen, which kit comprises:

(a) a source of said at least one antigen to said autoantibody;

(b) a substrate having immobilized thereto at least one antibody to said antigen;

(c) means for contacting said antigen source with said sample of body fluid, so as to obtain a mixture wherein said antigen is allowed to [substantially] bind with said autoantibody, when the latter is present in said sample;

(d) means for allowing said mixture to flow [relative] <u>along</u> [to] said substrate [so as to allow said mixture to contact] <u>and to interact with</u> said antibody immobilized to said substrate;

(e) labeling means to permit monitoring of binding of said autoantibody and said antigen present in said mixture; and

(f) means for monitoring said binding so as to provide an indication of the

presence of said autoantibody in said sample of body fluid.

120. A kit according to claim 115, which further comprises a source of at least one [substantially] non-immobilized antibody to said antigen and means whereby said non-immobilized antibody can be contacted with said antigen source and said sample of body fluid.

121. A kit according to claim 120, wherein said non-immobilized antibody is provided in [substantially] purified form.

126. A kit according to claim 115, wherein said substrate comprises an application zone for at least said sample of body fluid, which application zone is provided upstream [on said substrate relative to] <u>of</u> said immobilized antibody <u>on said substrate</u>, whereby said mixture is allowed to flow from said application zone along said substrate so as to interact with said immobilized antibody.

128. A kit according to claim 126, wherein said application zone further includes at least one [substantially] non-immobilized antibody to said antigen, and means whereby said mixture is obtained by contacting said sample of body fluid and said antigen with said non-immobilized antibody present in said application zone.

129. A kit according to claim 126, wherein means are provided whereby said antigen source and said sample of body fluid are contacted [substantially] remote from said substrate so as to provide said mixture and means whereby said mixture is subsequently contacted with said application zone.

130. A kit according to claim 129, wherein means are provided whereby [at least one reagent selected from] said antigen source, said sample of body fluid and at least one [substantially] non-immobilized antibody to said antigen, [is] <u>are</u> contacted [substantially] remote from said substrate so as to provide said mixture, and means whereby said mixture is subsequently contacted with said application zone.

132. A kit according to claim 115, wherein said immobilized antibody is provided in [substantially] purified form.

135. A kit according to claim 115, for screening said sample of body fluid for one said autoantibody, wherein said antigen includes a binding site to which either said autoantibody or said immobilized antibody can bind, whereby binding of said immobilized antibody to said binding site is [substantially] precluded where said autoantibody has previously [substantially] bound to said binding site.

137. A kit according to claim 136, wherein said antigen includes:

a first binding site to which either said first autoantibody or said first immobilized antibody can bind, whereby binding of said first immobilized antibody to said first binding site is [substantially] precluded where said first autoantibody has previously [substantially] bound to said first binding site; and

a second binding site to which either said second autoantibody or said second immobilized antibody can bind, whereby binding of said second immobilized antibody to said second binding site is [substantially] precluded where said second autoantibody has previously [substantially] bound to said second binding site;

wherein said first and second binding sites are [substantially] distinct sites on the antigen.

140. A kit according to claim 120, wherein said non-immobilized antibody is provided with said labeling means, which non-immobilized antibody is capable of binding to a site on said antigen [substantially] distinct from a binding site for either (i) said autoantibody or autoantibodies being screened or (ii) said immobilized antibody, whereby antigen is allowed to be [substantially] bound both to said immobilized antibody and to said non-immobilized antibody.

141. A kit according to claim 120 for screening said sample of body fluid for at least first and second autoantibodies to said antigen, wherein said non-immobilized antibody is capable of binding to a site on said antigen to which either said first or second autoantibody can bind and which is [substantially] distinct to a binding site on said antigen for said immobilized antibody, whereby antigen can be

ABSTRACT

A method and kit for screening a sample of body fluid for at least one autoantibody to at least one antigen. A source of at least one antigen to the autoantibody is provided. A substrate having immobilized thereto at least one antibody to the antigen is also provided. The antigen source is contacted with the sample of body fluid, so as to obtain a mixture wherein the antigen is allowed to substantially bind with the autoantibody, when the latter is present in the sample of body fluid. The mixture is allowed to flow relative to the substrate so as to allow the mixture to contact the antibody immobilized to the substrate. Labeling means are provided to permit monitoring of binding of the autoanitbody and the antigen present in the mixture, so as to provide an indication of the presence of the autoanitbody in the sample of body fluid.